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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/563,011 | 06/19/2006 | Beatrice Schaack | 284025US0XPCT | 8486 |

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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

| EXAMINER | |
|---|---|
| VIVLEMORE, TRACY ANN | |
| ART UNIT | PAPER NUMBER |
| 1635 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 10/10/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/563,011 | SCHAACK ET AL. | |
| | Examiner | Art Unit | |
| | Tracy Vivlemore | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15,17-21,24,25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-21,24,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

***Election/Restrictions***

Applicants' clarification that claims 6 and 8 recite SEQ ID NOs that are part of the elected invention is noted and these claims have been included in the examination.

Claims 16, 22, 23 and 26 have been canceled and new claim 27 has been added. Claims 1-15, 17-21, 24, 25 and 27 are pending and examined on the merits.

***Claim Rejections - 35 USC § 102***

The amendment to claim 1 removing limitation (a) is sufficient to overcome the 102 rejection over Wyatt.

***Claim Rejections - 35 USC § 103***

Claims 1-15, 17-21, 24, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt (US 6,440,738, of record) in view of Bass (Nature 2001, of record) and Fosnaugh et al. (US 2003/014732, of record).

The claims are directed to double stranded complementary oligonucleotides of 17-21 nucleotides that are targeted to human casein kinase 2. In specific embodiments, the oligonucleotide is targeted to SEQ ID NO: 26, the strands comprise 5' phosphate groups, have 3' overhangs of tt or aa, are 19-20 or 21-23 nucleotides in length, are

present in expression cassettes, vectors or cells, or are formulated as mixtures of oligonucleotides, including a mixture of oligonucleotides targeted to three different subunits. In other embodiments, siRNAs are combined in compositions with chemotherapeutic or antiviral agents.

Wyatt teaches antisense oligonucleotides targeted to the β-subunit of human casein kinase 2 which is represented by SEQ ID NOs: 3 and 17. Wyatt teaches at column 2 that human casein kinase 2 expression is involved in several types of cancer and in viral replication. At columns 27-28 Wyatt teaches that pharmaceutical compositions of antisense oligonucleotides can be combined with either chemotherapeutic or antiviral agents. In table 1, Wyatt teaches several antisense oligonucleotides, one of which, SEQ ID NO: 60, is targeted to a region sharing 16 nucleotides with the elected target region represented by SEQ ID NO: 26. Wyatt does not teach siRNAs targeted to the β-subunit of human casein kinase 2.

Bass teaches on page 429, first column, that RNA interference is a routinely used gene silencing technique that has proven to be more robust than antisense techniques by working more often, decreasing expression to lower levels than antisense oligonucleotides and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments. Bass further teaches in the same column that the discovery of short interfering RNAs that are functional in mammalian cells will inspire further research studies aimed at optimizing the use of siRNAs, as well as at understanding why conventional RNAi using longer dsRNA works in eggs and embryos. Bass speculates that, based on the huge impact the RNAi technique has had in studies of non-mammalian systems, use of siRNA in mammalian

cells could be just as far-reaching, with applications extending to functional genomics and therapeutics.

Fosnaugh et al. teach that siRNAs are made of a sense and antisense strand and are useful for a variety of therapeutic, diagnostic, agricultural, target validation, genomic discovery, genetic engineering and pharmacogenomic applications. Chemically-modified siRNAs are expected to improve various properties of siRNAs including increased *in vivo* nuclease resistance and/or improved cellular uptake. Specific embodiments of siRNAs and chemically modified siRNAs are taught in the figures and at pages 3-8, including 5' phosphate groups at paragraph 46, 3' overhangs at paragraph 17 and lengths of siRNAs of 19-25 nucleotides at paragraph 33. Figure 4 teaches the specific embodiment of tt overhangs. Paragraph 25 teaches expression vectors and cells comprising siRNAs. Paragraphs 195-200 teach siRNA compositions comprising formulations that allow cellular penetration and targeting of specific tissues or organs. In example 3, Fosnaugh et al. teach production of pools of siRNAs. Fosnaugh et al. is considered to comprise a detailed blueprint for how to make and use inhibitory siRNAs to target any known gene.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs targeted to the β subunit of human casein kinase 2 and to produce these siRNAs with 3' overhangs, 5' phosphates and stabilizing modifications as taught by Fosnaugh et al. One of ordinary skill in the art would have had a motivation to make siRNAs targeted to casein kinase 2 because Wyatt teaches the role of casein kinase 2 in cancers and viral replication and teaches that antisense oligonucleotides targeted to this gene are useful in inhibiting expression and because

Bass teaches that inhibition of gene expression using siRNAs has the advantages of working more often, decreasing expression to lower levels than antisense oligonucleotides and working at concentrations several orders of magnitude below the concentrations typically used in antisense experiments. One of ordinary skill in the art would have had a motivation to make these siRNAs with the features recited in the instant claims because Fosnaugh et al. explicitly teach the advantages of siRNAs having these characteristics. Because Wyatt teaches inhibition of casein kinase 2 by making and testing a multitude of oligonucleotides targeted throughout the gene sequence and because Fosnaugh et al. provide a detailed teaching of how to make and use siRNAs to any known gene, one of ordinary skill in the art would recognize that targeting an siRNA to SEQ ID NO: 26 with the siRNA sequences in claims 6 and 8 to be a matter of design choice and routine optimization to find siRNAs having the best properties for a desired application. Based on the suggestion of Wyatt that inhibitors of casein kinase 2 be combined with additional chemotherapeutic or antiviral agents, one of ordinary skill in the art would also combine siRNAs targeted to casein kinase 2 with these agents and based on the teaching by Fosnaugh et al. that multiple siRNAs can be combined into one composition, one of ordinary skill in the art would recognize that siRNAs to different targets could also be combined. One of ordinary skill in the art would have had a reasonable expectation of success in producing human casein kinase 2 siRNAs with 3' overhangs, 5' phosphates and stabilizing modifications because synthesis of nucleic acids containing modified nucleotides is routine and well-known in the art.

Thus, the invention of claims 1-15, 17-21, 24, 25 and 27 would have been obvious, as a whole, at the time the invention was made.

Claims 1-15, 17-19, 21 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over John et al. (US 2004/0023855, of record) in view of Fosnaugh et al. (US 2003/0143732, of record).

The claims are directed to double stranded complementary oligonucleotides of 17-21 nucleotides that are targeted to human casein kinase 2. In specific embodiments, the oligonucleotide is targeted to SEQ ID NO: 26, the strands comprise 5' phosphate groups, have 3' overhangs of tt or aa, are 19-20 or 21-23 nucleotides in length, are present in expression cassettes, vectors or cells, or are formulated as mixtures of oligonucleotides, including a mixture of oligonucleotides targeted to three different subunits. In other embodiments, siRNAs are combined in compositions with chemotherapeutic or antiviral agents.

John et al. teach nanoparticles suitable for delivery of therapeutic agents to cells and exemplify this with antisense oligonucleotides targeted to human casein kinase 2. At paragraph 127 John et al. teach that siRNAs have the advantage of being easy to design and can be based on any portion of a messenger RNA molecule. John et al. explicitly suggest the casein kinase 2 mRNA transcript be used to prepare a siRNA molecule. John et al. suggest making siRNAs targeted to human casein kinase 2 but do not produce siRNAs having overhangs, 5' phosphates or stabilizing modifications.

Fosnaugh et al. teach that siRNAs are made of a sense and antisense strand and are useful for a variety of therapeutic, diagnostic, agricultural, target validation,

genomic discovery, genetic engineering and pharmacogenomic applications. Chemically-modified siRNAs are expected to improve various properties of siRNAs including increased *in vivo* nuclease resistance and/or improved cellular uptake. Specific embodiments of siRNAs and chemically modified siRNAs are taught in the figures and at pages 3-8, including 5' phosphate groups at paragraph 46, 3' overhangs at paragraph 17 and lengths of siRNAs of 19-25 nucleotides at paragraph 33. Figure 4 teaches the specific embodiment of tt overhangs. Fosnaugh et al. is also considered to comprise a detailed blueprint for how to make and use inhibitory siRNAs to target any known gene. Paragraph 25 teaches expression vectors and cells comprising siRNAs. Paragraphs 195-200 teach siRNA compositions comprising formulations that allow cellular penetration and targeting of specific tissues or organs.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce siRNAs targeted to casein kinase 2 mRNA as suggested by John et al. with 3' overhangs, 5' phosphates and stabilizing modifications as taught by Fosnaugh et al. John et al. provide a motivation to make siRNAs targeted to human casein kinase 2 by explicitly suggesting they be produced and one of ordinary skill in the art would have been motivated to produce such siRNAs with the features recited in the instant claims because Fosnaugh et al. explicitly teach the advantages of siRNAs having these characteristics. Because John et al. suggests inhibition of casein kinase 2 by siRNAs and because Fosnaugh et al. provide a detailed teaching of how to make and use siRNAs to any known gene, one of ordinary skill in the art would recognize that targeting an siRNA to SEQ ID NO: 26 with the siRNA sequences in claims 6 and 8 to be a matter of design choice and routine optimization to find siRNAs

having the best properties for a desired application. Based on the teaching by Fosnaugh et al. that multiple siRNAs can be combined into one composition, one of ordinary skill in the art would recognize that siRNAs to different targets could also be combined. One of ordinary skill in the art would have had a reasonable expectation of success in producing human casein kinase 2 siRNAs with 3' overhangs, 5' phosphates and stabilizing modifications because synthesis of nucleic acids containing modified nucleotides is routine and well-known in the art.

Thus, the invention of claims 1-15, 17-19, 21 and 27 would have been obvious, as a whole, at the time the invention was made.

***Response to Arguments***

Applicants traverse the 103 rejections of record by arguing that antisense oligonucleotides and siRNAs are totally different molecules that use totally different mechanisms to inhibit gene expression, noting that antisense oligonucleotides are single stranded oligodeoxynucleotides complementary to the target mRNA sequence which primarily stimulate degradation of the mRNA via RNase H while siRNAs are short RNA duplexes that degrade the target RNA transcript by the endonuclease activity of RISC.

It is acknowledged that antisense oligonucleotides and siRNAs have different structures and mechanisms of action, however, both classes of molecule inhibit gene expression through targeting of an mRNA and, as evidenced by the teachings of Bass, those of ordinary skill in the art recognize that siRNAs possess several advantages over antisense oligonucleotides.

Applicants cite a 2008 paper discussing the binding thermodynamics of antisense oligonucleotides and siRNAs to assert there are fundamental differences in the sequence features which correlate with silencing efficacies for antisense oligonucleotides and siRNA, but provide no specific arguments relating this paper to the rejections of record. It is further noted that this paper is not relevant to the rejections of record because it was published several years after the instant filing date, while obviousness is evaluated with regard to the art at the time of filing.

Applicants argue that Wyatt does not provide teachings of siRNAs targeting the transcripts of the different CK2 subunits, that Bass teaches only the length of siRNAs and nothing is known about the sequence features of the siRNA which are capable of achieving specific inhibition of gene expression mammalian cells and that Fosnaugh et al. teach siRNAs targeted to a different gene, which would not help one of ordinary skill to make siRNA targeting the human CK2 subunits.

These arguments against the individual references are not persuasive because the rejection is for obviousness, which does not require that one reference provide all teachings. It is acknowledged that Wyatt does not teach siRNAs, the teachings of how to make siRNAs are found in Fosnaugh et al. Bass is not relied upon to teach sequence of siRNAs, it is relied upon to demonstrate that those in the art recognized the advantages of RNAi over antisense gene inhibition.

Applicants additionally argue that John et al. are totally silent about siRNA and teach only nanoparticles for the intracellular delivery of biologically active agents. This is incorrect; paragraph 127 of John et al. discusses siRNAs and specifically suggests siRNAs to CK2, "One advantage of using siRNA molecules is that such molecules are

very easy to design. In fact, siRNA molecules can be based on any portion of a messenger RNA molecule or transcript and still be effective in delivering a therapeutic effect in a target cell. As an example, the casein kinase 2 mRNA transcript can be used to prepare an siRNA molecule."

Applicants further argue that although many algorithms to design siRNAs were available at the time the invention was made, it was difficult to design siRNAs with high efficiency to its target, citing a paper published in 2007. This argument is not persuasive because the rejections of record are not predicated on use of algorithms to predict efficient siRNAs. Furthermore, it appears to be based on a misunderstanding of the cited reference. This reference discusses the difficulties in predicting *a priori* (i.e., without actually testing) which siRNAs will be efficient and which will not; it does not state that efficient siRNAs cannot be made and in fact refers on page 1787, column 2, to a test of 30 siRNAs wherein 17 inhibited expression by 80%.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Primary Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635